

## AMENDMENTS

### Amendments to the Claims:

This listing replaces all prior versions and listings of claims in the application:

### Listing of Claims:

1. (currently amended) A method for selecting a rationally designed siRNA for a target gene, wherein said rationally designed siRNA comprises 19 – 25 nucleoside base pairs, said method comprising:
  - (a) selecting a target gene, wherein the target gene comprises a target sequence;
  - (b) generating a set of candidate siRNA molecules, wherein each of said candidate siRNA molecules comprises an antisense region of at least 19 bases that are at least substantially complementary to a region of the target gene;
  - (c) applying at least one a criterion non-target specific criterion to each of said at least one candidate siRNA molecules sequence, wherein the at least one non-target specific criterion is selected from the group consisting of: (i) the number of A and U nucleotides present in the first five nucleotide positions at the 5' terminus of the antisense region is higher than that present in the last five nucleotide positions at the 3' terminus of the antisense region; (ii) the number of A and U nucleotides present in the first four positions at the 5' terminus of the antisense region is higher than that present in the last four positions at the 3' terminus of the antisense region; (iii) the number of A and U nucleotides present in the first three positions at the 5' terminus of the antisense region is higher than that present in the last three positions at the 3' terminus of the antisense region; (iv) the number of A and U nucleotides in the first two positions at the 5' terminus of the antisense region is higher than that present in the last two positions at the 3' terminus of the antisense region; and (v) the first 5' position of the antisense region has either an A or U nucleotide and the last 3' position of the antisense region has neither an A nor U nucleotide comprises the presence or absence of a particular nucleotide at at least one of sequence positions 1-19 of the siRNA, the at least one non-

~~target specific criterion increases a likelihood that said candidate siRNA sequence is functional, and the at least one candidate siRNA sequence comprises an antisense strand that is at least substantially complementary to a stretch of nucleotides of the target sequence; and~~

(d) ~~selecting a rationally designed a candidate siRNA as said siRNA for the target gene, if said candidate siRNA wherein said rationally designed siRNA comprises a sequence that satisfies said at least one non-target specific criterion.~~

2. (canceled)

3. (canceled)

4. (canceled)

5. (canceled)

6. (currently amended) A method for developing an siRNA algorithm for selecting a ~~rationally designed~~ siRNA, said method comprising:

(a) selecting a set of siRNA, wherein the set of siRNA comprises a plurality of siRNA that are directed against sequences in a target gene;

(b) determining the ability of each siRNA of said plurality of siRNA to silence the target gene;

(c) correlating the presence or absence of one or more ~~at least one~~ variables with said ability of each siRNA to silence said target gene, wherein said ~~at least one~~ one or more variables ~~is are~~ selected from the group consisting of total GC content, melting temperature of the siRNA, GC content at positions 15 –19, the presence or absence of a particular nucleotide at a particular position and the number of times that the same nucleotide repeats within a given sequence; and

(d) developing an algorithm for selecting siRNA that are capable of silencing a ~~target gene~~, wherein said algorithm comprises said one or more variables ~~at least one variable~~, and when the algorithm is applied to a candidate siRNA sequence the algorithm is capable of generating a value that is dependent on the satisfaction of said ~~at least one~~ or more variables

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~~and different values that are generated for different candidate siRNA sequences indicate a relative likelihood of functionality.~~

7. (canceled)

8. (canceled)

9. (canceled)

10. (canceled)

11. (canceled)

12. (canceled)

13. (canceled)

14. (canceled)

15. (canceled)

16. (canceled)

17. (canceled)

18. (canceled)

19. (canceled).

20. (canceled)

21. (canceled)

22. (canceled)

23. (canceled)

24. (canceled)

25. (canceled)

26. (canceled)

27. (currently amended) The method according to claim 6, wherein said algorithm ~~comprises two or more at least one variable~~ ~~comprises at least two~~ variables selected from the group consisting of: the total GC content, melting temperature of the siRNA, GC content at positions 15 -19, the presence or absence of one or more particular nucleotides at one or more particular positions, and the number of times that the same nucleotide repeats within a given sequence ~~and said algorithm comprises said at least two variables.~~

28. (currently amended) The method according to claim 27, wherein said algorithm ~~comprises three or more at least two variables~~ ~~comprise at least three~~ variables selected from the group consisting of: the total GC content, melting temperature of the siRNA, GC content at positions 15 -19, the presence or absence of one or more particular nucleotides at one or more particular positions, and the number of times that the same nucleotide repeats within a given sequence ~~and said algorithm comprises said at least three variables.~~

29. (currently amended) The method according to claim 28, wherein said algorithm ~~comprises four or more at least three variables~~ ~~comprise at least four~~ variables selected from the group consisting of: the total GC content, melting temperature of

the siRNA, GC content at positions 15 -19, the presence or absence of one or more particular nucleotides at one or more particular positions, and the number of times that the same nucleotide repeats within a given sequence ~~and said algorithm comprises said at least four variables.~~

30. (canceled)

31. (canceled)

32. (canceled)

33. (canceled)

34. (canceled)

35. (canceled)

36. (canceled)

37. (canceled)

38. (New) The method according to claim 1, wherein the criterion is: the number of A and U nucleotides present in the first five nucleotide positions at the 5' terminus of the antisense region is higher than that present in the last five nucleotide positions at the 3' terminus of the antisense region.

39. (New) The method according to claim 1, wherein the criterion is: the number of A and U nucleotides present in the first four positions at the 5' terminus of the antisense region is higher than that present in the last four positions at the 3' terminus of the antisense region.

40. (New) The method according to claim 1, wherein the criterion is: the number of A and U nucleotides present in the first three positions at the 5' terminus of the antisense region is higher than that present in the last three positions at the 3' terminus of the antisense region.
41. (New) The method according to claim 1, wherein the criterion is: the number of A and U nucleotides present in the first two positions at the 5' terminus of the antisense region is higher than that present in the last two positions at the 3' terminus of the antisense region.
42. (New) The method according to claim 1, wherein the criterion is: the first 5' position of the antisense region has either A or U and the last 3' position of the antisense region had neither A nor U.
43. (New) A method for selecting a siRNA for a target gene, wherein said siRNA comprises 19 – 25 nucleoside base pairs, said method comprising:
  - (a) selecting a target gene;
  - (b) generating a set of candidate siRNA molecules, wherein each of said candidate siRNA molecules comprises a sense region of at least 19 bases that are at least substantially similar to a region of the target gene;
  - (c) applying a set of one or more criteria selected from the group consisting of the presence of A at position 19 of the sense region, the presence of A at position 3 of the sense region, the presence of U at position 10 of the sense region, the presence of A at position 14 of the sense region, the absence of C at position 19 of the sense region, the absence of G at position 13 of the sense region, the absence of U at position 5 of the sense region and the absence of A at position 11 of the sense region; and
  - (d) selecting a candidate siRNA as said siRNA for the target gene, if said candidate siRNA satisfies said one or more criteria.

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44. (New) The method according to claim 43, wherein the set of one or more criteria includes the presence of A at position 19 of the sense region.
45. (New) The method according to claim 43, wherein the set of one or more criteria includes the presence of A at position 3 of the sense region.
46. (New) The method according to claim 43, wherein the set of one or more criteria includes the presence of U at position 10 of the sense region.
47. (New) The method according to claim 43, wherein the set of one or more criteria includes the presence of A at position 14 of the sense region.
48. (New) The method according to claim 43, wherein the set of one or more criteria includes the absence of C at position 19 of the sense region.
49. (New) The method according to claim 43, wherein the set of one or more criteria includes the absence of G at position 13 of the sense region.
50. (New) The method according to claim 43, wherein the set of one or more criteria includes the absence of U at position 5 of the sense region.
51. (New) The method according to claim 43, wherein the set of one or more criteria includes the absence of A at position 11 of the sense region.
52. (New) The method according to claim 43 further comprising applying one or more additional criteria selected from the group consisting of a GC content between about 30% and 52%, at least 2 A or U bases at positions 15 – 19 of the sense region, and a internal repeat that is not stable at greater than 50°C, and wherein said siRNA for the target gene satisfies said one or more additional criteria.

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53. (New) The method according to claim 43, wherein said candidate siRNA is selected as said siRNA for the target gene if said candidate siRNA satisfies at least two criteria selected from the group consisting of the presence of A at position 19 of the sense region, the presence of A at position 3 of the sense region, the presence of U at position 10 of the sense region, the presence of A at position 14 of the sense region, the absence of C at position 19 of the sense region, the absence of G at position 13 of the sense region, the absence of U at position 5 of the sense region, and the absence of A at position 11 of the sense region.
54. (New) The method according to claim 43, wherein said candidate siRNA is selected as said siRNA for the target gene if said candidate siRNA satisfies at least three criteria selected from the group consisting of the presence of A at position 19 of the sense region, the presence of A at position 3 of the sense region, the presence of U at position 10 of the sense region, the presence of A at position 14 of the sense region, the absence of C at position 19 of the sense region, the absence of G at position 13 of the sense region, the absence of U at position 5 of the sense region, and the absence of A at position 11 of the sense region.
55. (New) The method according to claim 43, wherein said candidate siRNA is selected as said siRNA for the target gene if said candidate siRNA satisfies at least four criteria selected from the group consisting of the presence of A at position 19 of the sense region, the presence of A at position 3 of the sense region, the presence of U at position 10 of the sense region, the presence of A at position 14 of the sense region, the absence of C at position 19 of the sense region, the absence of G at position 13 of the sense region, the absence of U at position 5 of the sense region, the absence of A at position 11 of the sense region, a GC content between about 30% and 52%, at least 2 A or U bases at positions 15 – 19 of the sense region, and a internal repeat that is not stable at greater than 50°C.
56. (New) The method according to claim 43, wherein said candidate siRNA is selected as said siRNA for the target gene if said candidate siRNA satisfies at least five

criteria selected from the group consisting of the presence of A at position 19 of the sense region, the presence of A at position 3 of the sense region, the presence of U at position 10 of the sense region, the presence of A at position 14 of the sense region, the absence of C at position 19 of the sense region, the absence of G at position 13 of the sense region, the absence of U at position 5 of the sense region, the absence of A at position 11 of the sense region, a GC content between about 30% and 52%, at least 2 A or U bases at positions 15 – 19 of the sense region, and a internal repeat that is not stable at greater than 50°C.

57. (New) The method according to claim 43, wherein said candidate siRNA is selected as said siRNA for the target gene if said candidate siRNA satisfies each of the following criteria: a GC content between about 30% and 52%, at least 2 A or U bases at position 15 – 19 of the sense region, A at position 19 of the sense region, A at position 3 of the sense region, a base other than C at position 19 of the sense region, a base other than G at position 13 of the sense region, and an internal repeat that is not stable at a temperature of greater than 50°C.
58. (New) The method according to claim 43, wherein said candidate siRNA is selected as said siRNA for the target gene if said candidate siRNA satisfies each of the following criteria: a GC content of between 30% and 52% and a base other than G at position 13 of the sense region.
59. (New) The method according to claim 43, wherein said candidate siRNA is selected as said siRNA for the target gene if said candidate siRNA satisfies each of the following criteria: a base other than C at position 19 of the sense region and a base other than G at position 13 of the sense region.
60. (New) The method according to claim 43, wherein said candidate siRNA is selected as said siRNA for the target gene if said candidate siRNA satisfies each of the following criteria: a GC content of between 30% and 52%, a base other than G at

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position 13 of the sense region and an internal repeat that is not stable at a temperature of greater than 50°C.